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ORIGINAL ARTICLE

Utility of rapid on-site evaluation for needle core biopsies and fine-needle aspiration cytology done for diagnosis of mass lesions of the liver

Saloni Walia, MD*, Manju Aron, MD, Eugenia Hu, SCT, Shefali Chopra, MD

Keck Medical Center, University of Southern California, Los Angeles, California

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KEYWORDS
Rapid onsite evaluation;
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Background Fine-needle aspiration (FNA) and core biopsy (CB) are used to diagnose liver lesions. Rapid onsite evaluation (ROSE) can improve the adequacy of the procedures and help triage diagnostic material appropriately. There are very few studies evaluating the role of ROSE for CB and FNA of mass lesions of the liver.
Methods Liver cases with ROSE material from 2007 to 2017 were retrieved and reviewed. The ROSE material was re-evaluated by 2 cytopathologists who were blinded to the final diagnosis. Data including age, number of lesions, number of passes, adequacy assessed at time of procedure, and diagnosis made by cytopathologist on ROSE material at time of re-review was compiled.
Results A total of 82 cases were identified; 33 were primary lesions (group A) and 49 were metastatic lesions (group B). ROSE done by cytotechnologist at time of procedure showed an adequacy rate of 84%. During re-review of ROSE material by cytopathologists, the overall adequacy rates were similar, although the adequacy rates in group B increased (to 100% from 92%) and it dropped in group A (from 73% to 52%). The overall accuracy rate was 90%. Hepatocellular adenoma, regenerative nodules, well-differentiated hepatocellular carcinoma, and angiosarcoma were not possible to diagnose on smears alone during ROSE.
Conclusions ROSE for liver lesions is useful for assessing adequacy. Certain lesions cannot be accurately diagnosed on ROSE alone. ROSE material when assessed by cytopathologist can improve adequacy rate and possibly decrease number of nondiagnostic specimens in group A, though the cost effectiveness needs to be assessed.

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*Corresponding author: Dr. Saloni Walia, MD; University of Southern California, Keck Medical Center, HC4 1450 San Pablo Street, Health Sciences Campus, Los Angeles, CA 90033; Tel.: +1 323 409 4606; Fax: +1 323 442 9993.
E-mail address: saloni.b.walia@gmail.com (S. Walia).

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Introduction

Liver is a common site of metastasis; common primary tumor sites include lung, gastrointestinal tract, breast, uterus, prostate, and melanoma.[1,2] Although metastatic malignancies are more common in the liver, primary liver lesions also occur. Management of mass lesions in the liver may require morphologic evaluation in the form of fine-needle aspiration (FNA), and/or core biopsy (CB), to establish a diagnosis, as well as to aid in staging the tumor.[3]

FNA or biopsy of liver mass is performed either percutaneously under computed tomography or ultrasound guidance or via endoscopic ultrasound (EUS)—guided technique. Because of the small volume of specimen procured during this procedure, however, there is always a chance that the lesion is not adequately sampled—or even completely missed.[4] Assessment of adequacy of the material obtained during FNA/CB can be performed at the time of procedure with rapid onsite evaluation (ROSE), using cytological evaluation of FNA smears and/or touch preparations (TPs).

ROSE has been shown to improve the adequacy rates in lung, thyroid, soft tissue, liver, and head and neck FNAs—increasing the sensitivity, and decreasing the number of passes per procedure.[5-7] This, in turn, lowers patient morbidity and reduces medical cost by preventing repeat procedures.[8] An additional advantage includes triage of specimen for ancillary testing like microbiology studies, flow cytometry, and molecular testing.[9] Multiple studies have shown that the preliminary diagnosis provided during ROSE compares favorably with the final diagnosis in multiple organ systems including lymph nodes, pancreas, bile duct/gallbladder, liver, mediastinum/lung, adrenal, spleen, and kidney.[10] Though the diagnostic value of ROSE in liver FNAs has been evaluated by Ceyan et al,[7] it has never been evaluated at any center in the Unites States. The utility of ROSE in core biopsies of liver lesions has been previously evaluated in a single study as part of a larger investigation looking at various other organ systems.[11] Adequacy and accuracy of ROSE comparing primary liver masses to metastatic liver lesions has never been evaluated. The aim of this study was to assess the role of ROSE in determining adequacy and accuracy of diagnosis in both primary and metastatic liver lesions on both FNA and TP.

Materials and methods

Pathology database of the Keck Hospital of the University of Southern California was searched from 2007 through 2017 for cases of liver biopsies and FNAs after institutional review board approval. Only cases in which ROSE was performed at the time of the procedure and where slides were available for review were included in this study.

Data were compiled including patient demographics, type of procedure, number of passes, number and size of the lesion(s), adequacy evaluation during ROSE, and the final diagnosis. ROSE was performed on air-dried Diff-Quik stained smears by cytotechnologists at the time of the procedure. The remainder of the cytology slides were stained with Papanicolaou stain after alcohol fixation. All except 2 FNAs cases (1 case of a primary liver lesion and the other case of a metastatic liver mass) had formalin-fixed paraffin embedded cell blocks for evaluation. There was inadequate material for cell block preparation in both of these cases. The core needle biopsies were fixed in formalin, paraffin-embedded, and stained using hematoxylin and eosin.

All slides prepared for ROSE were re-evaluated by 2 cytopathologists, who were blinded to the final diagnosis. Both adequacy and accuracy were assessed and compared with both the cytotechnologists' evaluation for adequacy and the final diagnosis for accuracy. Data were compiled and evaluated.

Results

A total of 82 patients were included in the study; 33 patients had primary liver lesions (group A) and 49 patients had metastatic liver masses (group B). Results are summarized in Table 1.

In group A, the median age was 69 years (range: 45-92 years), and the male:female ratio was 6:5. In 13 cases a single mass lesion was identified, and 17 cases had 2 or

Table 1 Demographic data for groups with primary and metastatic liver lesions.

	Primary liver masses	Metastatic liver masses
Total number	33	49
Median age, years	69	69
Sex, M/F	18/15	25/24
Single/multiple masses	13/17 (n = 30)	11/36 (n = 47)
Median size of the largest lesion, cm	6.5 (n = 31)	4.05 (n = 38)
Median number of passes	3 (n = 23)	3 (n = 39)
Percutaneous approach/endoscopic ultrasound	25/8	44/5
Number of adequate specimens on initial adequacy assessment by cytotechnologist	24	35
Touch preparation/FNA	22/11	29/20

more lesions. Two patients did not have any discrete mass and no data on the number of lesions were available for 1 patient. In group B, the median age was 69 years (range: 45-95 years) and the male:female ratio was 25:24. Eleven patients had a single mass, 36 had multiple masses, no identifiable mass was present in 1 patient, and no data were available in 1 patient.

The median sizes of the tumors in group A and B were 6.5 cm and 4.1 cm, respectively. The average number of passes performed to obtain adequate material was 3 in both groups. No correlation was identified between the size of the lesion, and number of passes performed (Pearson product-moment correlation coefficient: −0.158).

Twenty-two of the 33 cases (66.6%) in group A were TPs of core biopsies and the remaining 11 (33.3 %) were FNAs (Table 2). In group B, 29 of the 49 cases (59%) were TPs of core biopsies and 20 were FNAs. Twenty-four of the cases in group A, and 44 in group B, were biopsied percutaneously using image guidance. All the remaining cases in both groups were biopsied using EUS.

In group A, ROSE by cytotechnologists was adequate in 73% (24/33) of the cases as per pathology report. On re-review of the cases in group A by the cytopathologist, the adequacy rate dropped to 52% (17 of 33). As all these FNAs/core biopsies were done for mass lesions, the presence of benign-appearing hepatocytes alone on ROSE

Table 2 Adequacy and accuracy performed on ROSE material in primary liver lesions and comparison with final diagnosis.

Number	Type of specimen FNA/CB	Adequacy as performed by cytotechnologist at time of procedure	Adequacy performed by cytopathologist on re-review of ROSE material	Diagnosis by cytopathologist on ROSE material alone	Final diagnosis
1	CB	Adequate	Not adequate	Benign hepatocytes	High grade dysplasia
2	CB	Adequate	Adequate	Adenocarcinoma	Intrahepatic cholangiocarcinoma
3	CB	Adequate	Not adequate	No malignant cells seen	No malignant cells seen
4	FNA	Not adequate	Not adequate	Benign glandular and spindle cells	Benign glandular and spindle cells
5	CB	Adequate	Adequate	HCC	Moderately differentiated HCC
6	FNA	Adequate	Not adequate	No malignant cells seen	No malignant cells seen
7	CB	Not adequate	Not adequate	Benign hepatocytes	Well differentiated HCC
8	FNA	Adequate	Adequate	Hemangioma	Hemangioma
9	FNA	Not adequate	Not adequate	No malignant cells identified	Benign ductal cells
10	CB	Adequate	Not adequate	No malignant cells seen	Ischemic necrosis
11	FNA	Not adequate	Not adequate	Benign hepatocytes	Benign hepatocytes
12	FNA	Not adequate	Not adequate	Benign hepatocytes	Benign hepatocytes
13	FNA	Adequate	Adequate	Adenocarcinoma	Intrahepatic cholangiocarcinoma
14	FNA	Not adequate	Not adequate	No malignant cells seen	No malignant cells seen
15	CB	Adequate	Adequate	Adenocarcinoma	Intrahepatic cholangiocarcinoma
16	CB	Adequate	Adequate	HCC	Moderately differentiated HCC
17	CB	Adequate	Adequate	HCC	HCC
18	CB	Adequate	Adequate	Adenocarcinoma	Intrahepatic cholangiocarcinoma
19	CB	Adequate	Adequate	Adenocarcinoma	Intrahepatic cholangiocarcinoma
20	CB	Adequate	Adequate	Adenocarcinoma	Intrahepatic cholangiocarcinoma
21	CB	Adequate	Adequate	HCC	HCC
22	FNA	Adequate	Not adequate	Benign hepatocytes	Well differentiated HCC
23	CB	Adequate	Adequate	Neuroendocrine tumor	Mixed acinar neuroendocrine carcinoma
24	CB	Adequate	Adequate	Adenocarcinoma	Intrahepatic cholangiocarcinoma
25	CB	Adequate	Adequate	Neuroendocrine carcinoma	Poorly differentiated neuroendocrine carcinoma
26	CB	Not adequate	Not adequate	Benign hepatocytes	Regenerative nodule
27	CB	Adequate	Adequate	Hemangioma	Hemangioma
28	CB	Adequate	Not adequate	Benign hepatocytes	Regenerative nodule
29	CB	Adequate	Adequate	Adenocarcinoma	Intrahepatic cholangiocarcinoma
30	FNA	Not adequate	Not adequate	Atypical epithelial cells	Rare atypical epithelial cells
31	FNA	Not adequate	Not adequate	Benign hepatocytes	Benign hepatocytes
32	CB	Adequate	Adequate	Poorly differentiated malignant neoplasm favor carcinoma	Angiosarcoma
33	CB	Adequate	Not adequate	Benign hepatocytes	Adenoma

Abbreviations: CB, core biopsy; FNA, fine-needle aspiration; HCC, hepatocellular carcinoma.

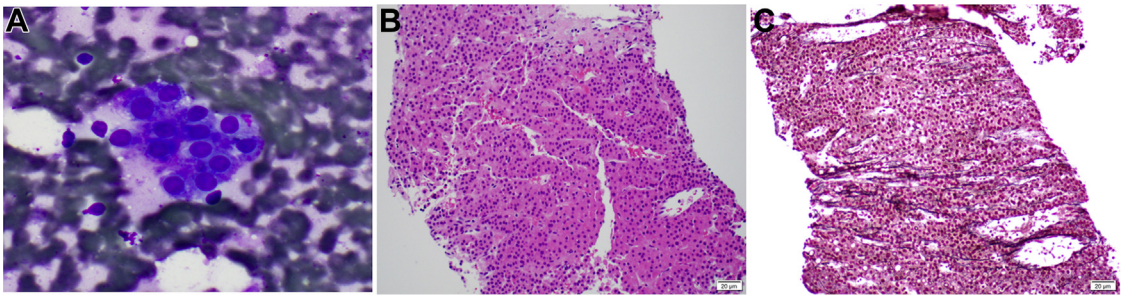

Figure 1 Well-differentiated hepatocellular carcinoma (WD-HCC). A, ROSE material showing benign appearing hepatocytes with ample cytoplasm, and round regular nuclei. No endothelial riming, transgressing vessels or atypia is identified (400x). B, Hematoxylin and eosin section showing lack of portal tracts, increased thick-walled arteries, and broadening of the trabeculae (200x). C, Reticulin stains shows loss of staining and confirms the increased thickness of the trabeculae (200x).

material was not considered adequate by the cytopathologist. Of the 14 cases called inadequate on ROSE by the cytopathologist, a diagnosis explaining a mass lesion could not be rendered in 9 cases, even after reviewing all material available including additional Papanicolaou stained slides and cell block or needle core biopsy. Eight of these cases were FNAs and one was a CB.

Follow-up was available in 3 of the 9 cases that were inadequate even on final diagnosis. All these cases were FNAs which had subsequent resections and were diagnosed as well-differentiated hepatocellular carcinoma (WD-HCC), focal nodular hyperplasia, and inflammatory pseudotumor. Seven cases that were inadequate at the time of ROSE but where a diagnosis could be rendered on reviewing all the material included 1 case each of hepatic adenoma, high-grade dysplastic nodule, and ischemic necrosis and 2 cases each of regenerative nodule and WD-HCC.

The accuracy rate was 71% (17 of 24) in group A. The 7 cases that could not be accurately diagnosed on ROSE material included a case of dysplastic nodule, 2 cases of regenerative nodules, 2 cases of WD-HCC (Fig. 1) 1 hepatic adenoma, and 1 angiosarcoma (Fig. 2). Even though these 7 cases could not be accurately diagnosed, it was possible to accurately categorize benign versus malignant in 21 out of 24 (88%) cases.

In group B, 92% (45 of 49) of the cases were called adequate during ROSE performed at time of procedure by cytotechnologists, and 8% (4 of 49) of the cases were called inadequate. Forty-five of the metastatic lesions were adenocarcinomas, 1 malignant melanoma (Fig. 3), 1 poorly differentiated neuroendocrine carcinoma (Fig. 4), 1 B-cell lymphoma (Fig. 5), and 1 thymic carcinoma. On re-review of the ROSE material by the cytopathologist, all the 49 cases were adequate (100%). In the 4 cases called inadequate on initial ROSE, the malignant cells were few in number and therefore likely missed by the cytotechnologist. One was a case of metastatic thymic carcinoma (Fig. 6), and the remaining 3 cases were metastatic adenocarcinomas (Figs. 7 and 8). The accuracy rate was 100% in the metastatic setting with the correct clinical history.

The overall adequacy of both groups A and B combined was 80% (66 of 82) and overall accuracy was 90% (66 of 73) on re-review of ROSE material by cytopathologist.

Discussion

There is an increase in detection of liver lesions thanks to increased and widespread use of imaging modalities.[12] Ultrasound-guided percutaneous and endoscopic liver

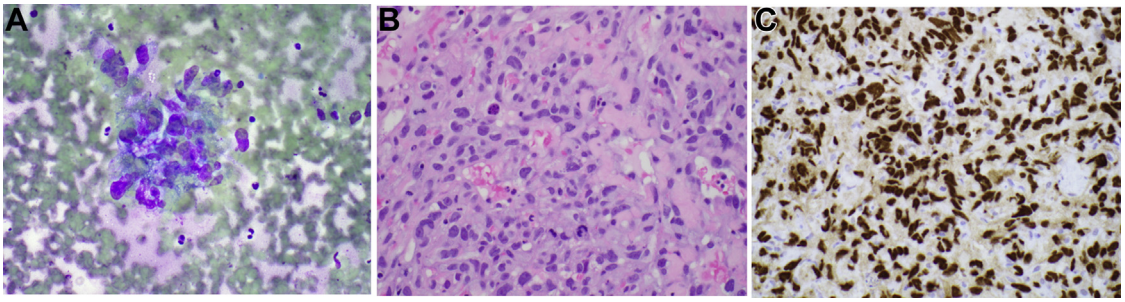

Figure 2 Angiosarcoma. A, Touch preparation showing disorganized group of malignant cells with vacuolated cytoplasm, large irregular nuclei, and prominent nucleoli in a bloody background. No vasoformative features are identified (400x). B, Hematoxylin and eosin section shows large atypical epithelioid cells with intraluminal red blood cells. Frequent mitoses are identified (200x). C, Positive ERG immunostain (20x).

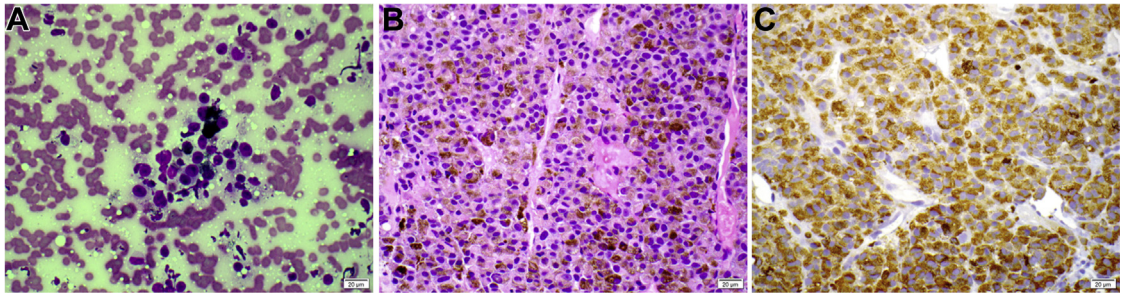

Figure 3 Metastatic melanoma. A, ROSE smear shows a group of malignant cells with intra-cytoplasmic pigment granules, large round nuclei and prominent nucleoli (200x). B, Hematoxylin and eosin—stained core biopsy section shows numerous pigment laden malignant cells (200x). C, Positive S100 immunostain (200x).

biopsy procedures have high sensitivity, specificity, and accuracy rate when diagnosing mass lesions of the liver.[13,14] Studies also have shown a high overall accuracy in diagnosing liver lesions by FNA cytology. In a retrospective study looking at over 4,000 cases, including primary benign and malignant liver lesions and metastatic lesions, the sensitivity of FNA was 97% when compared with histopathology.[15] ROSE can further improve the adequacy rates, thereby increasing the sensitivity and decreasing the number of passes per procedure. This is especially important in certain locations in the liver (such as the dome, that is technically challenging) for biopsy procedures where ROSE can help decrease the number of passes.

Although liver FNA/CB has a limited role in the diagnosis of HCC because of well-defined imaging criteria for the diagnosis of HCC,[16-18] there has been a rise in liver biopsy for primary lesions over the years. Liver biopsy is performed when the imaging criteria are not completely diagnostic for HCC[19] or for lesions thought not to be HCC on imaging. Cysts or hemangiomas may occur at multiple foci within the liver, and may be biopsied, as these may not be easy to distinguish from metastatic lesions by radiology alone.[20,21] CB may also be done for lesions favored to be adenomas and focal nodular hyperplasias to make management decisions.[22] Recently, biopsies of HCC are also being done to guide or stratify treatment with newer agents

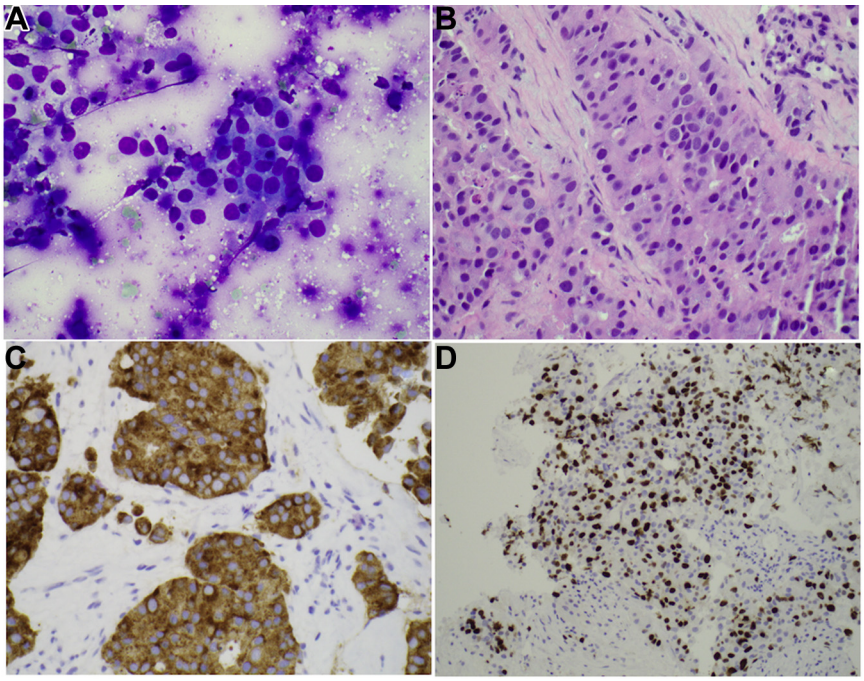

Figure 4 Poorly differentiated neuroendocrine tumor. A, Diff-Quik—stained slides show a group of large atypical cells with large nuclei, apoptotic figures and delicate cytoplasm, which is disrupted in rare cells (400x). B, Hematoxylin and eosin—stained section showing trabecular arrangement of malignant cells. These cells have fine chromatin, moderate cytoplasm, and lack prominent nucleoli (200x). C, Positive synaptophysin immunostain (200x). D, Ki67 immunnostain with proliferative index of 50% (200x).

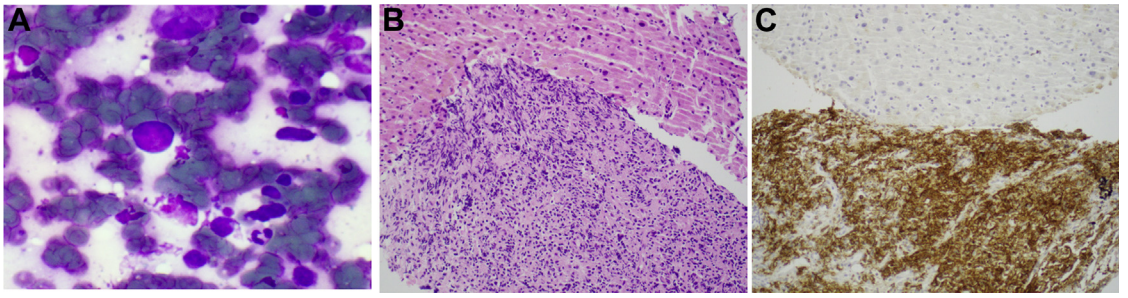

Figure 5 B-cell lymphoma. A, ROSE slide shows medium sized lymphocyte with fine chromatin and absence of prominent nucleolus (400x). B, Hematoxylin and eosin–stained section shows a mass formed of small to medium lymphocytes infiltrating the hepatic parenchyma (100x). C, Positive CD20 immunostain (100x).

like tivantinib and other MET tyrosine kinase receptor inhibitors.[23]

Ceyhan et al[7] studied the utility of ROSE in the diagnosis of liver lesions in FNA samples and found the sensitivity of onsite cytopathological examination and conventional smear to be 92.8%. No similar studies have been done in the United States to evaluate the utility of ROSE in liver lesions. There is only one study evaluating the role of ROSE on core biopsies of various organ systems, which included 61 cases from the liver.[11]

The adequacy rate of ROSE by cytopathologists in our study was 52% for primary lesions and 100% for metastatic lesions, with an overall adequacy rate of 80%; this is somewhat lower than the 2 prior studies. It is important to note, however, that the final adequacy in our series was also lower: 24 of 33 (73%) in group A. There were 9 cases in group A in which the diagnosis could not explain a mass lesion even after reviewing all the material (final diagnosis). Eight of these cases were FNAs and one was a core needle biopsy.

A diagnosis explaining a mass lesion was possible only on 2 of 11 FNAs done in group A. One case was a hemangioma and the other was a cholangiocarcinoma. Three of the FNAs where a diagnosis was not possible on FNA proved to be WD-HCC, focal nodular hyperplasia, and inflammatory pseudotumor on resection, highlighting the challenge of diagnosing these lesions on FNAs alone and the need of a CB with ancillary studies for definitive diagnosis in such cases. Out of the 22 needle cores, only 1 specimen could not identify a reason for mass lesion even on the final diagnosis. This finding reiterates the superiority of needle cores in diagnosing primary liver lesions because

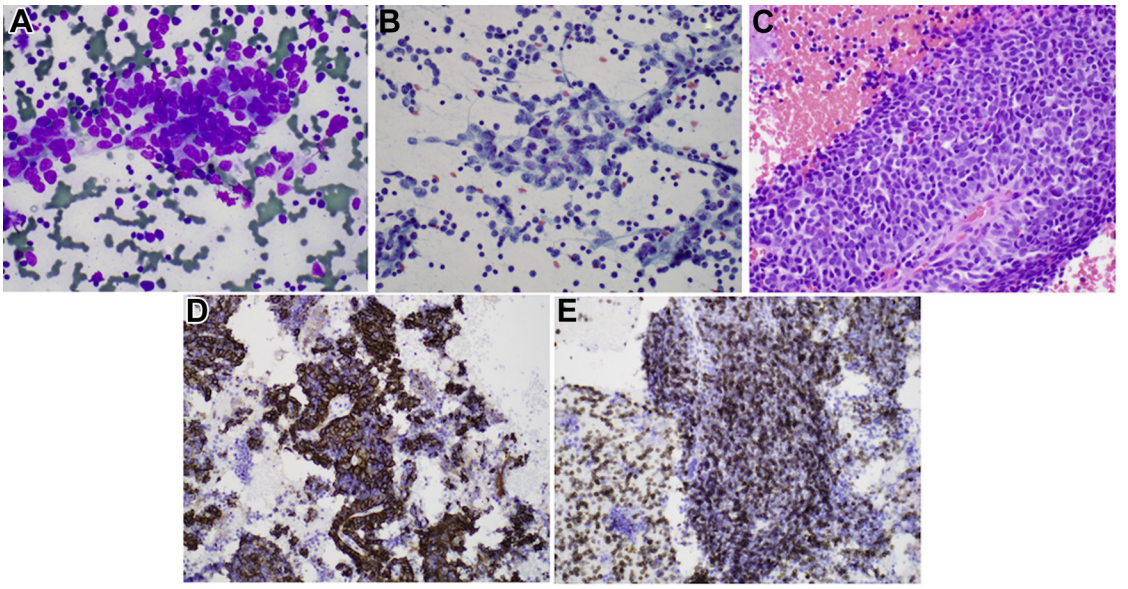

Figure 6 Metastatic thymic carcinoma. A, Diff-Quik–stained smear showing a group of atypical spindle cells admixed with small lymphocytes (400x). B, Papanicolaou-stained smear shows spindle cells with irregular nuclear contours and clumped chromatin in a background of mature lymphocytes (400x). C, Hematoxylin and eosin–stained cell block section shows a large cluster of overlapping spindle cells along with lymphocytes (400x). D, Keratin AE1/AE3 immunohistochemical stain shows circumferential membranous staining of the epithelial cells (200x). E, CD5 immunostain is positive in the malignant cells (200x).

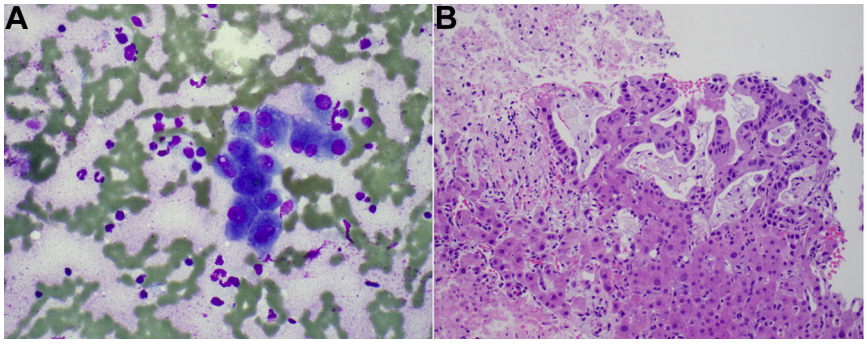

Figure 7 Metastatic adenocarcinoma. A, ROSE smear showing small group of large atypical cells with moderate amount of finely vacuolated cytoplasm. Large nuclei with prominent nuclei are seen (400x). B, Hematoxylin and eosin−stained slide shows a focus of adenocarcinoma with gland formation and necrosis is identified infiltrating the liver parenchyma (bottom right) (200x).

it may be challenging to unequivocally diagnose focal nodular hyperplasias, hepatic adenomas, regenerative nodules, and WD-HCCs by FNA. On FNAs and cell block material, these lesions are characterized by hepatocytes without significant atypia and trabeculae that are 2 cells thick. The diagnosis of hepatic adenoma can only be made on needle core biopsies, because they are characterized by absent portal tracts and preserved hepatic trabeculae thickness, which are highlighted by the reticulin stain. Therefore, in cases where the ROSE material from a mass lesion shows benign appearing hepatocytes, it might be more prudent to reflex to a needle core biopsy, thereby obviating the need for a repeat procedure. Also, in case of hepatic adenomas, ancillary stains would be needed to subtype the adenoma,[24] since beta catenin−mutated adenomas have a risk of malignant transformation in approximately half of the cases.[25]

The diagnosis of well-differentiated hepatocellular carcinoma and dysplastic nodules can be challenging on ROSE.[26] Although there are published diagnostic criteria for the diagnosis of dysplasia and low-grade HCC by cytology preparations,[27] our experience has been similar to prior studies where histology as well as special and immunohistochemical stains are necessary to make the diagnosis of WD-HCC.[28]

In our study, 2 cases of WD-HCC could not be accurately diagnosed since they lacked high nuclear-to-cytoplasmic ratio, endothelial rimming, and/or transgressing vessels, which are required for an unequivocal diagnosis of HCC on ROSE. Ancillary studies including a reticulin stain and glypican-3 were required in addition to hematoxylin and eosin−stained sections. Poorly differentiated HCC can be difficult to distinguish from other poorly differentiated epithelial and mesenchymal neoplasms on smears at the time of ROSE, but often yield enough material for adequacy assessment.

The only case of angiosarcoma we had in our study although diagnosed as adequate and malignant, could not be accurately classified on ROSE, and required the evaluation of hematoxylin and eosin sections and immunostains (including ERG) for a definite diagnosis.

Moderately differentiated HCC (4 cases), cholangiocarcinoma arising in intrahepatic bile ducts (8 cases), and hemangioma (2 cases) could be accurately diagnosed during ROSE in the current study. Although the smears from the hemangiomas showed only small caliber benign vessels on the touch preparation slide, the diagnosis of hemangioma was possible in conjunction with the radiological impression of a hemangioma.

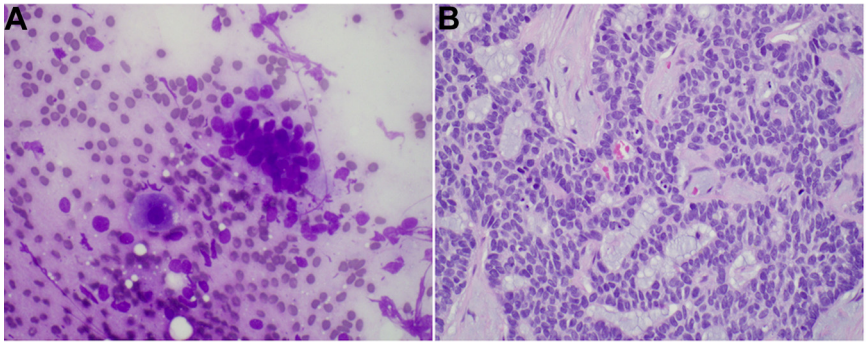

Figure 8 Metastatic adenoid cystic carcinoma. A, Diff-Quik−stained smear showing a disordered cluster of malignant cells (200x). A single benign appearing hepatocyte is also identified adjacent to the cluster. B, Hematoxylin and eosin−stained slide shows basaloid cells in a cribriform pattern surrounding cyst-like spaces (200x).

In comparison in the metastatic setting, FNAs alone might be sufficient for diagnosis. The adequacy and accuracy rates were similar for both touch imprints and FNAs of liver lesions in the metastatic setting. ROSE adequacy and accuracy is very high (both 100%) in metastatic lesions.

It might be useful to have a cell block/core needle biopsy in certain metastatic tumors—for example, neuroendocrine tumors. Though the diagnosis of well-differentiated neuroendocrine tumor can most often be made on ROSE, a cell block/core needle biopsy would be needed to perform Ki-67 immunohistochemical stain to grade these tumors. Grading of these tumors can be done on cell block material, as shown in prior studies[29,30] with the sensitivity and specificity being 64% and 87%, respectively, at the current recommended level of 2%. In the study by Laskiewick et al,[29] the authors found that 22 of the 26 specimens had concordance with the surgical specimen, and, among the incorrectly graded specimens, two had only 50 cells. Though a core needle biopsy is not essential to grade these tumors, it is important to have sufficient material on the cell block for grading neuroendocrine tumors. Also, it can sometimes be challenging to differentiate well-differentiated from poorly differentiated neuroendocrine tumors just on ROSE material, and histology and ancillary immunohistochemical stains might be needed.[31] A liver mass might be the initial presentation of well-differentiated neuroendocrine tumors and that might be the only diagnostic material available in such cases.

Earlier studies have shown the overall accuracy of the ultrasound-guided biopsy procedure to be dependent on the size of the mass lesion,[32] whereas more recent studies show no correlation between the 2.[33] In our study, no relationship was identified between the size of the lesion, the number of passes performed for procuring diagnostic material, and the adequacy at the time of ROSE.

The overall adequacy rates when both groups were combined were similar—84% for the cytotechnologist and 80% when done by the cytopathologist. Adequacy assessment on re-review of ROSE material when done by the cytopathologist on the metastatic lesions increased, whereas it decreased in the primary liver lesions group, as having benign appearing hepatocytes alone was not considered diagnostic criteria for adequacy in setting of a mass lesion.

Having a cytopathologist perform adequacy on primary liver lesions might possibly increase the final adequacy of the specimens in group A and FNAs can be converted to CBs where necessary at the time of the initial procedure itself.

Accuracy rates for an cytopathologist on ROSE material alone were 71% in primary lesions, and 88% of the cases could be accurately classified as benign versus malignant. Accuracy rate was 100% in metastatic lesions.

Conclusion

ROSE is a valuable tool in determining the adequacy and decreasing the number of passes, both for FNA biopsies and CBs. It is important to re-emphasize that the presence of benign-appearing hepatocytes alone should not be used to call a specimen adequate at time of ROSE. In such instances, it may be prudent to suggest to the radiologist to perform a CB. Adequacy assessment by a cytopathologist at the time of ROSE of primary liver lesions is likely to yield more adequate material than when ROSE is performed by a cytotechnologist—although the cost effectiveness of a cytopathologist performing adequacy and comparing it with the cost of repeat procedures in primary liver lesions needs to be assessed.

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